

## **General Practitioners' Section**

# **Swine-Origin Influenza A (H1N1) : An Update**

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### **Abstract**

Beginning in March 2009, an outbreak of influenza in North America was found to be caused by a new strain of influenza virus, designated Influenza H1N1 2009, which is a reassortant of swine, avian and human influenza viruses. Over a thousand total cases were identified with the first month, chiefly in the United States and Mexico, but also involving several European countries. On April 15 and April 17, 2009, novel swine-origin influenza A (H1N1) virus (S-OIV) was identified in specimens obtained from two epidemiologically unlinked patients in the United States. The same strain of the virus was identified in Mexico, Canada, and elsewhere. On June 11, 2009, the World Health Organization raised its pandemic alert level to the highest level, phase 6, indicating widespread community transmission on at least two continents. In India the first case was detected in May 2009 in Hyderabad and by mid August there have been more than one thousand five hundred cases tested positive and more than 45 patients have died. *Our previous article on Swine Flu in April issue of this journal briefly discussed this disease.* In this article we will review this disease with updated information on the epidemiology, clinical manifestations, diagnosis, treatment and preventive strategies for pandemic H1N1 influenza A virus infection.

### **Introduction**

In March and April 2009, an outbreak of respiratory illnesses was first noted in Mexico, which was eventually identified as being related to H1N1 influenza A. The outbreak spread rapidly to the United States, Canada, and throughout the world as a result of airline travel. As of July 27, 2009, over 134,500 laboratory-confirmed cases had been reported in over 100 countries. Since early July, the World Health Organization has ceased closely tracking the number of cases, since it has become extremely difficult for countries to continue such monitoring in the setting of widespread community transmission. Furthermore, even with close

tracking, the true number of cases are many fold higher than the numbers of confirmed cases. The disease has spread to more than 168 countries as of August 2009. The US tops the list with over 50, 000 H1N1 cases reported, more than 22 Indian cities have reported positive cases and if infection spreads at this rate it may impact global GDP by 3 per cent. The focus has shifted to following trends of illness rather than individual cases in countries with widespread disease, and to close monitoring of cases only in newly affected countries. Updated information can be found at the websites of the United States Centers for Disease Control and Prevention (<http://www.cdc.gov/h1n1flu/update.htm>) and the World Health Organization (<http://www.who.int/csr/disease/swineflu/en/index.html>)

*Age distribution* — A typical feature of

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newly emergent pandemic influenza strains is that severe infection occurs disproportionately in individuals who are not at the extremes of age. In contrast, seasonal influenza is more likely to cause severe disease in infants, young children, and elderly individuals. From late March to late April 2009 in Mexico, 87 per cent of deaths and 71 per cent of cases of severe pneumonia occurred in patients between the ages of 5 and 59 years; by comparison, an average of 17 per cent of deaths and 32 per cent of severe pneumonia were attributed to influenza infection during earlier influenza epidemics.

### **The Virus**

Influenza virus, an enveloped virus of the Orthomyxoviridae family, has a unique capacity for genetic variation that is based in two molecular features of the virus family.<sup>1</sup> First of all, the surface proteins of the virus are highly variable, able to mutate up to 50% of their amino acid sequence and still perform their functions.

The fact that its haemagglutinin is 27.2% different and its neuraminidase is 18.2% different in amino acid sequence from the 2008 H1N1 and vaccine virus strains give Influenza H1N1 2009 significant pandemic potential. Further evolution of the virus toward a more efficient agent of human disease may yet enable it to produce a major pandemic.

### **Transmission**

*Person-to-person transmission* — In contrast to previous outbreaks of swine influenza viruses described above, the pandemic of H1N1 influenza A infection that began in March 2009 appears to involve sustained human-to-human transmission, as suggested by the large number of patients with respiratory illnesses identified within a short period of time at various locations

around the world.<sup>3</sup> Influenza virus is present in respiratory secretions of infected persons. As a result, influenza virus can be transmitted through sneezing and coughing via large-particle droplets. Transmission via contact with surfaces that have been contaminated with respiratory droplets or by aerosolized small-particle droplets may also occur. In addition to respiratory secretions, certain other bodily fluids (e.g., diarrhoeal stool) should also be considered potentially infectious. Based on analysis by the World Health Organization using early data from the outbreak in Mexico and other countries, transmissibility appears substantially higher compared with seasonal influenza. The secondary attack rate of the strain causing this pandemic is estimated to be 22 to 33 per cent, compared with 5 to 15 per cent for seasonal influenza.<sup>4</sup> Since the duration of shedding of pandemic H1N1 influenza A virus is currently unclear, the estimated duration of shedding is based upon what is known for seasonal influenza virus. Patients with pandemic H1N1 influenza A virus infection are likely to be contagious from one day prior to the development of signs and symptoms until resolution of fever. Although the precise incubation period has not been established for pandemic H1N1 influenza A infection, it could range from one to seven days, and most likely from one to four days.<sup>5</sup> However, because the duration of shedding has not been established, individuals should be considered contagious until seven days after illness onset. Longer periods of shedding may occur in children (especially young infants), elderly adults, patients with chronic illnesses, and immunocompromised hosts. There is no risk of becoming infected with influenza virus from eating pork.

### **Clinical Features**

The signs and symptoms of influenza

caused by pandemic H1N1 influenza A virus are similar to those of seasonal influenza, although gastrointestinal manifestations appear to be more common with pandemic H1N1 influenza A.<sup>6</sup> The most common clinical findings of the 2009 H1N1 influenza A pandemic have been fever, cough, sore throat, malaise, and headache; vomiting and diarrhoea have also been common, both of which are unusual features of seasonal influenza.<sup>6</sup> Other frequent findings have included chills, myalgias, and arthralgias. The severity appears to be less than what was observed during the influenza pandemic of 1918 to 1919. In New York City, 95 per cent of patients with pandemic H1N1 influenza A have met the case definition for influenza-like illness (subjective fever plus cough and/or sore throat).<sup>5</sup> In contrast, approximately one third of patients seen at two hospitals in Mexico had no fever at presentation.<sup>7</sup> Certain groups, such as infants, elderly individuals, and immunocompromised hosts, may have atypical presentations. The full range of complications of infection with pandemic H1N1 influenza A is not yet known, although fatal and non-fatal cases of pneumonia have occurred.

### **Children**

Symptoms of severe disease in infants and young children may include apnoea, tachypnoea, dyspnoea, cyanosis, dehydration, altered mental status, and extreme irritability. Young children (e.g., < 5 years of age) are at increased risk for influenza complications.<sup>8</sup> In California, the most common risk factors for influenza complications were chronic lung disease (asthma or chronic obstructive pulmonary disease, 37 per cent), immunosuppressive conditions (17 per cent), cardiac disease (17 per cent), pregnancy (17 per cent), diabetes mellitus (13 per cent), and obesity (13 per

cent). Although elderly patients are considered to be at an increased risk for complications of influenza, pandemic H1N1 influenza A infection in such individuals have been uncommon to date possibly as a result of preexisting immunity against antigenically similar influenza viruses that circulated prior to 1957.

### **Complications**

Few bacterial infections have been detected in patients with pandemic H1N1 influenza A; these include empyema, necrotizing pneumonia and bacterial coinfection, as well as ventilator-associated pneumonia.<sup>6</sup> Common pulmonary complications include primary viral pneumonia, secondary bacterial pneumonia, and exacerbation of COPD and bronchial asthma. Extra pulmonary complications are myositis, rhabdomyolysis, myoglobinuria, myocarditis and pericarditis. At times central nervous system (CNS) complications may arise which include encephalitis, transverse myelitis, and Guillain-Barré syndrome and Reye's syndrome. During the 2009 pandemic, rapidly progressive pneumonia, respiratory failure, and acute respiratory distress syndrome have been reported in some cases in Mexico.<sup>9-11</sup> Between late March and late April 2009, 2155 cases of severe pneumonia, including 821 hospitalizations and 100 deaths, were reported to the epidemiologic surveillance network in Mexico.<sup>10</sup> In contrast to the experience in Mexico, pneumonia has been uncommon among patients with pandemic H1N1 influenza A in the United States.<sup>12</sup> Among 18 patients in Mexico requiring hospitalization for pneumonia due to pandemic H1N1 influenza, all had fever, cough, dyspnoea or respiratory distress, increased serum lactate dehydrogenase levels, and bilateral patchy pneumonia.<sup>11</sup> Increased creatine kinase levels and

lymphopenia were also common findings, occurring in 62 and 61 per cent of patients, respectively. Twelve patients required mechanical ventilation and seven died.

### **Pregnant Women**

In the United States during the 2009 H1N1 influenza A pandemic, increased rates of hospitalization have been observed among pregnant women compared with the general population.<sup>13</sup> In addition, six influenza-related deaths in pregnant women were reported to the US Centers of Disease Control and Prevention between April 15 and June 16, 2009; all deaths occurred in women who developed pneumonia and acute respiratory distress syndrome requiring mechanical ventilation. Other countries have also reported an increased risk of severe influenza among pregnant women during the 2009 pandemic, particularly during the second and third trimesters.<sup>14</sup>

### **Diagnosis**

Guidelines for the diagnosis of pandemic H1N1 influenza A virus have been released by the United States Centers for Disease Control and Prevention (CDC). Updated recommendations can be found at the CDC website (<http://www.cdc.gov/swineflu/>). Testing for pandemic H1N1 influenza A should be considered in individuals with an acute febrile respiratory illness (a measured temperature of 100°F or higher and recent onset of at least one of the following: rhinorrhoea, nasal congestion, sore throat, or cough) or sepsis-like syndrome.<sup>5</sup> Priority for testing should be given to,<sup>5</sup> those who require hospitalization and those who are at high risk for severe complications. Not all individuals with suspected pandemic H1N1 influenza A need to have the diagnosis confirmed, particularly if the illness is mild or the person resides in an area with

confirmed cases. Recommendations on whom to test may differ by state or community.

### **Specimens**

To establish the diagnosis of pandemic H1N1 influenza A, an upper respiratory sample (nasopharyngeal swab, nasal swab, throat swab, combined oropharyngeal/nasopharyngeal swab, or nasal aspirate) should be collected. In intubated patients, an endotracheal aspirate should also be obtained. Swabs with a synthetic tip (e.g., polyester or Dacron) and an aluminium or plastic shaft should be used. Swabs with cotton tips and wooden shafts are not recommended. Swabs made of calcium alginate are not acceptable. The collection vial in which the swab is placed should contain 1 to 3 mL of viral transport media. Specimens should be placed in viral transport media and placed on ice (4°C) or refrigerated immediately for transportation to the laboratory. Once the samples arrive in the laboratory, they should be stored either in a refrigerator at 4°C or in a -70°C freezer. If a -70°C freezer is not available, they should be kept refrigerated, preferably for ≤ 1 week. Specimens should be sent on dry ice to the designated health laboratory in clearly labelled containers.

### **Recommended Tests**

The recommended test to confirm the diagnosis of pandemic H1N1 influenza A virus is real-time reverse transcriptase (RT)-PCR for influenza A, B, H1, and H3. However, in some countries, RT-PCR is performed only when the results will substantially impact clinical management or when there is a recognized public health benefit.

The strain of H1N1 influenza A virus associated with the 2009 pandemic tests positive for influenza A and negative for H1 and H3 by real-time RT-PCR. Isolation of pandemic H1N1 influenza A virus using

culture is diagnostic, but culture is usually too slow to help guide clinical management. A negative viral culture does not exclude pandemic H1N1 influenza A infection.

### **Rapid Antigen Tests**

Clinicians may consider using rapid influenza antigen tests as part of their evaluation of patients suspected of having pandemic H1N1 influenza A, but results should be interpreted with caution.<sup>15</sup> Confirmation of pandemic H1N1 influenza A infection can only be made by real-time reverse-transcriptase (RT)-PCR or culture. The sensitivity and specificity of rapid antigen testing for pandemic H1N1 influenza A virus infection have not been established, and poor sensitivity has already been demonstrated for seasonal influenza. Based on limited data, the sensitivity of rapid antigen testing for detecting pandemic H1N1 influenza is probably similar to, or lower than, the sensitivity for detecting seasonal influenza.<sup>15</sup>

Among 39 patients with pandemic H1N1 influenza A confirmed by RT-PCR, 20 had a positive rapid antigen test using the QuickVue Influenza A+B (Quidel) assay (sensitivity 51 per cent).<sup>16</sup> Twelve of 19 patients who had seasonal H1N1 influenza confirmed by RT-PCR had a positive rapid antigen test (sensitivity 63 per cent). In the same study, the specificity of rapid antigen testing was 99 per cent for patients with either the pandemic strain or a seasonal strain of H1N1 influenza A.

Certain rapid influenza antigen tests that are commercially available can distinguish between influenza A and B viruses.<sup>15</sup> Thus, a patient with only influenza B virus infection would not be suspected of having pandemic H1N1 influenza A virus infection. In contrast, a patient with a positive rapid antigen test for influenza A may be considered a probable case if he or she meets the other criteria. A

negative rapid influenza test does not exclude infection.

*Immunofluorescent antibody testing* - Direct or indirect immunofluorescent antibody testing (DFA or IFA) can distinguish between influenza A and B.<sup>17</sup> Thus, a patient with a positive DFA or IFA may be considered a probable case if he or she meets the other criteria. A negative DFA or IFA does not exclude pandemic H1N1 influenza A infection since these tests have unclear sensitivity to detect this virus.

### **Definitions**

*Case definitions* — Definitions are changing as we learn more about this virus and the syndromes it causes. Cases in the United States are confirmed by diagnostic testing at the Centers for Disease Control and Prevention.<sup>17</sup>

*Influenza-like illness* (ILI) is defined as fever (temperature of 100°F [37.8°C] or greater) with cough or sore throat in the absence of a known cause other than influenza.

The following case definitions have been provided by the United States Centers for Disease Control and Prevention.

- A confirmed case of pandemic H1N1 influenza A is defined as an individual with an ILI with laboratory-confirmed H1N1 influenza A virus detection by real-time reverse transcriptase (RT)-PCR or culture.
- A probable case of pandemic H1N1 influenza A is defined as an individual with an ILI who is positive for influenza A, but negative for H1 and H3 by RT-PCR

Pandemic H1N1 influenza A may be suspected in an individual who does not meet the definitions of confirmed or probable pandemic H1N1 influenza A, but has an ILI and an epidemiologic link (e.g., likely

exposure to a confirmed or probable case within the past seven days).

### **Antiviral Therapy**

The vast majority of strains of pandemic H1N1 influenza A virus circulating in 2009 appear sensitive in vitro to the neuraminidase inhibitors, oseltamivir and zanamivir, but all strains tested have been resistant to amantadine and rimantadine.<sup>18,19</sup> However, there are no reported studies yet on the clinical benefits of antiviral therapy. As of July 22, 2009, five isolates of pandemic H1N1 influenza virus with resistance to oseltamivir have been detected from patients in Denmark, Japan, Hong Kong, and Canada.<sup>19</sup> No tested isolates have been resistant to zanamivir, and the four patients whose clinical courses have been reported recovered without complications.<sup>19</sup> The United States Centers for Disease Control and Prevention (CDC) has released guidelines for the use of antivirals for patients with confirmed or suspected pandemic H1N1 influenza A virus infection and close contacts.<sup>18</sup> Therapy should be started as soon as possible, since evidence of benefit is strongest for seasonal influenza when treatment is started within 48 hours of illness onset.<sup>18</sup> Some studies of hospitalized patients have demonstrated benefit even when therapy for seasonal influenza is started > 48 hours after onset of illness. In patients who are more than mildly ill, we would initiate therapy even past 48 hours of symptoms.<sup>18</sup>

**Adults** — antiviral therapy is recommended for:<sup>18</sup>

- All hospitalized patients with confirmed, probable, or suspected pandemic H1N1 influenza A virus infection and patients at increased risk for complications. During the current pandemic, patients with mild illness do not need to be tested or treated unless they have risk factors for complications.<sup>18</sup> However, the decision

of whether to initiate antiviral therapy for each patient should be based upon the clinician's judgement and on what is known about the benefits of therapy for seasonal influenza. In areas with limited antiviral availability, local public health officials might provide additional guidance regarding their prioritization.

### **Antiviral Prophylaxis**

Indications in adults — The indications for post-exposure antiviral prophylaxis are based upon close contact with a patient who is a confirmed, probable, or suspected case of pandemic H1N1 influenza A infection. The United States Centers for Disease Control and Prevention states that post-exposure antiviral prophylaxis can be considered for,

- Close contacts who are at high risk for complications of influenza (e.g., individuals with certain chronic medical conditions, ≥ 65 years of age, pregnant women) of a confirmed, probable, or suspected case.
- Health care workers, public health workers, or first responders who were not using appropriate personal protective equipment during close contact with a confirmed, probable, or suspected patient during that person's infectious period.

Pre-exposure antiviral prophylaxis should only be used in limited situations, and in consultation with local medical or public health authorities. Certain individuals who have ongoing occupational risk for exposure (e.g., healthcare workers, public health workers, first responders) who are also at increased risk of influenza complications should follow guidelines for personal protective equipment stringently or consider temporary reassignment.

*Choice of agent* - When antiviral prophylaxis is indicated, either oseltamivir

or zanamivir should be used. The dosing of antivirals for pandemic H1N1 influenza A infection is the same as for seasonal influenza in adults .

*Indications during pregnancy*- The United States Centers for Disease Control and Prevention states that antiviral chemoprophylaxis can be considered in pregnant women who are close contacts of individuals with suspected, probable, or confirmed pandemic H1N1 influenza A infection. Some experts advocate prophylaxis for all women exposed to a patient with pandemic H1N1 influenza A during the second or third trimester of pregnancy.

Zanamivir is probably the drug of choice for prophylaxis given its limited systemic absorption. Oseltamivir is an alternative agent for women with a contraindication to zanamivir, such as asthma or chronic obstructive pulmonary disease. Oseltamivir and zanamivir are Pregnancy Category C drugs, reflecting that clinical studies have not been done to assess the safety of their use during pregnancy.

*Indications in children* - The US Food and Drug Administration has issued an emergency use authorization for clinicians to use oseltamivir or zanamivir during the current pandemic when indicated in children younger than the ages for which they have been approved.<sup>20</sup>

Postmarketing reports have identified rare, but serious neuropsychiatric events in children with influenza who are taking oseltamivir.

*Paediatric dosing* - The dosing of antivirals for pandemic H1N1 influenza A prophylaxis is the same as for seasonal influenza. The dosing of oseltamivir for infants <1 year of age depends upon the age of the infant:

- Age < 3 months — Not recommended

unless the patient is critically ill.

- Age 3 to 5 months — 20 mg once daily
- Age 6 to 11 months — 25 mg once daily

*Duration of prophylaxis* - Antiviral prophylaxis should be continued for 10 days after the last known exposure to an individual with confirmed pandemic H1N1 influenza A. In individuals who receive pre-exposure prophylaxis, the antiviral drug should be given during the potential exposure period and continued for 10 days after the last known exposure to a patient with confirmed pandemic H1N1 influenza A. Post-exposure prophylaxis should be considered for contact during the infectious period (one day before until seven days after the case's onset of illness). If the contact occurred more than seven days earlier, prophylaxis is not necessary.

The most common side effects of Tamiflu are mild to moderate nausea and vomiting. Tamiflu is generally well tolerated. People with the flu, particularly children and adolescents, may be at an increased risk of self injury and confusion shortly after taking Tamiflu and should be closely monitored for signs of unusual behaviour. Efficacy of Tamiflu in the treatment of subjects with chronic cardiac disease and/or respiratory disease has not been established. Efficacy of Tamiflu for treatment or prophylaxis has not been established. The safety and pharmacokinetics in patients with severe hepatic impairment have not been evaluated. Rare cases of anaphylaxis and serious skin reactions including toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme have been reported in post marketing experience with Tamiflu. Tamiflu should be stopped and appropriate treatment instituted if an allergic-like reaction occurs or is suspected.

## **Pandemic Concerns**

The pandemic concerns of H1N1 influenza are because of the following factors. Since this virus is a new strain, human populations have not been vaccinated or naturally immunized. Also, as the viruses reassort (i.e. swap genes) and new viruses that are a mix of swine, human and/or avian influenza viruses emerge, the development of a new vaccine takes time. There is a lack of data related to transmission patterns and effectiveness of current influenza treatments and reliable forecasts cannot be made.

## **Critical Measures**

Critical measures include the following. Avoid crowding patients together, promote distance between patients. Perform hand hygiene. Wear personal protective equipments which include high efficiency masks (ideally N95 mask or else triple layer surgical mask), gowns, goggles, gloves, cap and shoe cover. If suspected swine flu occurs, isolation is recommended for infected individuals and household contacts. If dedicated isolation room with HEPA filter and negative pressure is not available then patients can be kept in a well ventilated isolation ward with beds kept one meter apart.

## **Treatment**

*Choice of antiviral* - For patients requiring treatment, we recommend either zanamivir or oseltamivir.<sup>18</sup> Zanamivir is contraindicated in patients with asthma or chronic obstructive pulmonary disease. During this pandemic, in patients suspected to have influenza but who have no epidemiologic link to pandemic H1N1 influenza A, the recommended treatment is with a neuraminidase inhibitor. However, in locations where oseltamivir-resistant seasonal H1N1 influenza A virus is circulating, it is suggested that the neuraminidase inhibitor be zanamivir rather than

oseltamivir. In such a setting, for patients who are unable to take zanamivir, we suggest the addition of an adamantane (rimantadine or amantadine) to oseltamivir.<sup>18</sup> Antiviral therapy should be continued for five days, as with seasonal influenza.

*Pregnancy* - Seasonal and pandemic strains of influenza cause more severe disease and an increased rate of mortality among pregnant women.<sup>21</sup> Cases of severe pandemic H1N1 influenza A have been reported in pregnant women, including a fatal case in a woman with psoriasis and mild asthma who was diagnosed at 35 weeks' gestation. Oseltamivir and zanamivir are Pregnancy Category C drugs, reflecting that clinical studies have not been done to assess the safety of their use during pregnancy.<sup>18</sup> No adverse events have been shown to be caused by oseltamivir or zanamivir among women who received these agents during pregnancy or among infants who were exposed while in utero, although there are limited data.<sup>22</sup> Pregnant women who meet current case definitions for confirmed, probable, or suspected pandemic H1N1 influenza A infection should receive antiviral therapy with oseltamivir, since the potential benefit outweighs the theoretical risk to the foetus.<sup>21</sup> Oseltamivir is recommended over zanamivir because only the former agent is systemically absorbed. Treatment should be initiated as early as possible, and should not be withheld while awaiting results of diagnostic testing or in situations in which testing is not performed.<sup>21</sup> Although the benefits of antiviral therapy are expected to be greatest when initiated within the first 48 hours following symptom onset, treatment should be administered even to pregnant women who present > 48 hours after illness onset, particularly in those requiring hospitalization. In addition to antiviral therapy, use of acetaminophen is important when fever is

present, since hyperthermia during the first trimester has been associated with neural tube defects and other birth defects.<sup>21,23</sup> In addition, fever during labour is a risk factor for neonatal seizures, encephalopathy, cerebral palsy, and neonatal death.<sup>21,23</sup>

*Children* - Oseltamivir is approved in the United States for the treatment of influenza A and B viral infections in individuals  $\geq 1$  year of age. Zanamivir is approved for the treatment of influenza A and B viral infections in individuals  $\geq 7$  years of age. However, the US Food and Drug Administration has issued an emergency use authorization for clinicians to use oseltamivir or zanamivir in younger children, when indicated, during the current pandemic.<sup>20</sup> Limited safety data on oseltamivir treatment in infants  $<1$  year of age suggest that severe adverse reactions are rare.<sup>18</sup> Children who may have influenza infection should not take aspirin or aspirin-containing products, such as bismuth subsalicylate (PeptoBismol), due to the increased risk of Reye syndrome.<sup>18</sup> Patients with pandemic H1N1 influenza A who develop pneumonia should be treated empirically for community-acquired pneumonia (CAP). In hospitalized patients with severe CAP requiring intensive care unit admission who also have either necrotizing/cavitary infiltrates or empyema, methicillin-resistant *Staphylococcus aureus* (MRSA) infection should be suspected and treated in addition to other potential causes).

*Breastfeeding* - Infants who are ill with pandemic H1N1 influenza A should continue to breastfeed.<sup>21</sup> The United States Centers for Disease Control and Prevention recommends that lactating women with pandemic H1N1 influenza A infection continue to provide breastmilk for their infants since the passive transfer of antibodies against the virus can protect the infant.

*Preventive Measures* - In regions with

known cases of pandemic H1N1 influenza A, all patients with an acute febrile respiratory illness (a measured temperature of 100°F or higher and recent onset of at least one of the following: rhinorrhoea, nasal congestion, sore throat, or cough) should be managed using the following infection control guidelines. The same precautions should be taken with patients with an acute febrile respiratory illness in a region in which cases have not been identified, but who have had contact within the previous seven days with an individual with confirmed, probable, or suspected pandemic H1N1 influenza A virus or who have travelled to a region with confirmed cases within the previous seven days. As the pandemic evolves, the ability to use epidemiologic links may be lost.

Patients with suspected or confirmed pandemic H1N1 influenza A virus infection should be placed directly into single patient rooms with the door kept closed. Air from the patient's room can be vented directly outside or can be recirculated after high-efficiency particulate (HEPA) filtration.

*Face masks and respirators* — The effectiveness of face masks and N95 respirators in preventing transmission of pandemic H1N1 influenza A is not known. Face masks do not seal tightly to the face and are used to prevent large droplets from coming into contact with the user's mouth or nose. N95 respirators fit tightly and filter out small particles. The optimal use of N95 respirators requires fit testing, training, and medical clearance. N95 respirators are not recommended for children or individuals with facial - close contact with individuals who might be ill and being in crowded settings should be avoided whenever possible. For occupational exposures in non-healthcare settings, face masks or N95 respirators are generally not recommended. Use of a face

mask or N95 respirator is NOT recommended for the routine care of individuals who are not at increased risk for influenza complications in the community or at home, even when caring for an individual with an influenza-like illness (fever with cough or sore throat). However, use of a face mask or N95 respirator should be considered by individuals who are at increased risk for influenza complications and who are required to be the caregiver of an infected individual. N95 respirators should be used by caretakers during administration of respiratory treatments (e.g., using a nebulizer or inhaler).

### **Vaccine**

It is hoped that a vaccine to protect against pandemic H1N1 influenza A will be available by mid-October 2009. Individuals may require more than one injection of the H1N1 influenza A vaccine (e.g., one month apart). Since Swine flu was declared to be a pandemic, or global outbreak, by the World Health Organization in June, pharmaceuticals have been racing to get their vaccines ready. The clinical trials of vaccines against the pandemic strain of swine flu have started in Australia, China, Germany, the U.K. and the U.S., according to the World Health Organisation (WHO). Some of these vaccines could complete the process for regulatory approval and be ready for public use by next month. India has hitherto not been producing flu vaccines. But now three leading manufacturers - Serum Institute of India in Pune, Bharat Biotech in Hyderabad and Panacea Biotec in Delhi - are seeking to make the swine flu vaccine within the country. But it looks like the indigenous vaccine will not be ready for several months more, and even subsequently it may be available only in limited quantities. Moreover, under the WHO scheme, the Serum Institute is committed to providing at least 10 per cent of its swine flu vaccine

production for use in other countries, according to a report that has appeared in the latest issue of the Indian edition of the magazine Technology Review.

The production capacity of the world's large flu vaccine manufacturers is already committed for many months to meeting the advance contracts from rich countries for the swine flu vaccine. The WHO is doing its best to ensure that some amount of the pandemic vaccine becomes available to the developing countries.

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#### **INTENSIVE VS. CONVENTIONAL GLUCOSE CONTROL IN CRITICALLY ILL PATIENTS**

In this study, adults who were expected to require treatment in the intensive care unit on 3 or more consecutive days were randomly assigned to undergo intensive blood glucose control (target range, 81 to 108 mg per deciliter (4.5 to 6.0 mmol per liter) or conventional blood glucose control (180 mg per deciliter [10.0 mmol per liter]). The primary end point was death from any cause within 90 days after randomization. Intensive glucose control increased mortality among the patients.

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